

CORRESPONDENCE

Comment on: Incidence, clinicopathological features, and clinical outcomes of low HER2 expressed, inoperable, advanced, or recurrent gastric/gastroesophageal junction adenocarcinoma



Anti-human epidermal growth factor receptor 2 (HER2)-based therapy is the standard treatment approach in advanced HER2-positive gastric and gastroesophageal adenocarcinoma. HER2 test result discordance rates of 12%¹-23%² between local and central testing as well as a putative detrimental effect of trastuzumab application on overall survival (OS) in patients without HER2 over-expression/HER2 amplification [immunohistochemistry (IHC) 0, 1+, or 2+ and *in situ* hybridization (ISH) negative]¹ corroborate the importance of central HER2 testing in clinical practice. Encouraging overall response rates with trastuzumab-deruxtecan (19%-37%) in pre-treated, HER2-low (IHC 1+ or IHC 2+ and ISH negative) patients³ also highlight the necessity of a uniform definition and assessment of HER2-low disease in clinical trials investigating HER2-targeting antibody—drug conjugates.

We have read with interest the article “Incidence, clinicopathological features, and clinical outcomes of low HER2 expressed, inoperable, advanced, or recurrent gastric/gastroesophageal junction adenocarcinoma” by Nakayama et al.⁴ The authors report a HER2-positive, HER2-low, and HER2-negative frequency of 23%, 21%, and 56%, respectively, among 734 Asian patients in their unicentric, retrospective analysis. Median OS was comparable between HER2-low and HER2-negative disease (15.2 versus 15.0 months, $P = 0.788$), while a HER2-low status turned out to be inferior to HER2-positive cases (15.2 versus 20.2 months, $P = 0.002$).⁴

In 2020, we published the findings from the GASTRIC-5 registry of the Austrian Group of Medical Tumor Therapy (AGMT) including the HER2-positivity rate, the discordance rate between local and central HER2 testing, and clinical outcome with front-line trastuzumab-based therapy in HER2-positive advanced gastric and gastroesophageal adenocarcinoma ($n = 183$).¹

While local assessment of the HER2 status within the GASTRIC-5 registry (HER2 positive: 27%, HER2 low: 23%, HER2 negative: 50%) was in line with the unicentric HER2 status pattern among Asian patients reported by Nakayama et al.,⁴ blinded central HER2 status evaluation revealed a considerably higher frequency of HER2-low cases (HER2 positive: 21%, HER2 low: 56%, HER2 negative: 23%). For local testing, different immunohistochemical assays and primary antibodies were used: HercepTest, Roche 4B5, and clone CB11. For central immunohistochemical retesting the HER-2/neu 4B5 PATHWAY (Roche) and in case of score 2+ the HER-2 Dual ISH DNA Probe Cocktail Assay (Roche) was used.

HER2 test results from a retrospective analysis at the MD Anderson Cancer Center among patients with advanced gastric and gastroesophageal adenocarcinoma ($n = 204$) also suggest a higher frequency of HER2-low disease (32%)⁵ compared to the Asian cohort.⁴ In line with the findings reported by Nakayama et al.,⁴ OS was comparable between HER2-negative and HER2-low disease within the GASTRIC-5 registry, independent from locally (median 13.5 versus 9.5 months, $P = 0.247$) or centrally (median 12.2 versus 11.3 months, $P = 0.773$, Figure 1) assessed HER2 test results.

A retrospective evaluation of the screening data from the KEYNOTE-811 trial and DESTINY-Gastric-01 trial (central review of HER2 status was mandatory) may further elucidate the frequency of the putative predictive biomarker—HER2 low—in advanced gastric and gastroesophageal adenocarcinoma. In comparison to categorical scoring of the HER2 status by IHC, evaluation of HER2 messenger RNA expression by real-time quantitative PCR offers the advantage of reporting results as continuous variables and might help defining HER2-low disease in patients with gastrointestinal tumors that derive benefit from anti-HER2-based therapy.⁶

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Available online 19 March 2024

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<https://doi.org/10.1016/j.esmoop.2024.102973>
DOI of original article: <https://doi.org/10.1016/j.esmoop.2023.101582>

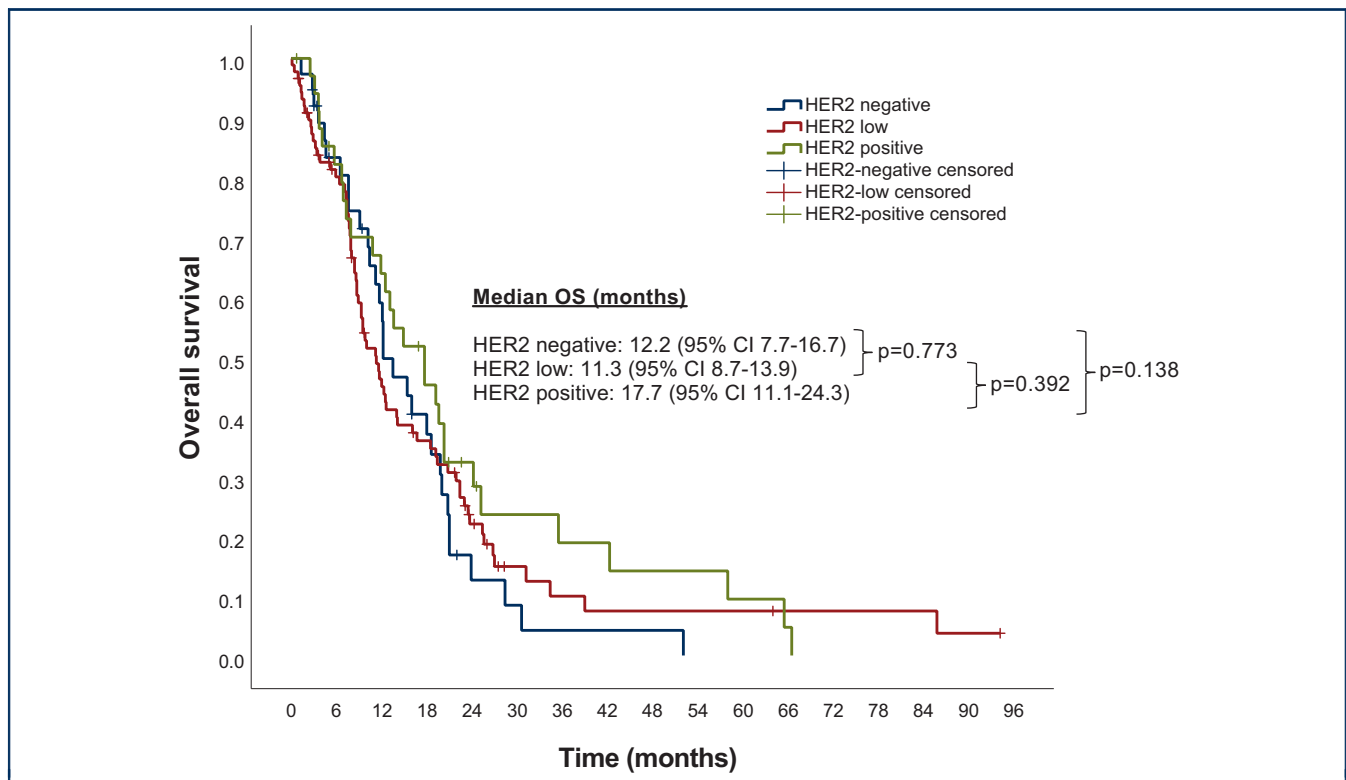


Figure 1. Kaplan–Meier curves for overall survival according to centrally assessed HER2 status (HER2 negative versus HER2 low versus HER2 positive) in the GASTRIC-5 registry. Tick marks on the curves represent censored patients. CI, confidence interval; HER2, human epidermal growth factor receptor 2.

FUNDING

Roche supported the registry financially, but had no input into central test evaluation, statistical analysis, data interpretation, or writing of the report (no grant number).

DISCLOSURE

FH: honoraria: Lilly, Pierre Fabre, Amgen, Servier, Daiichi Sankyo, BMS, Merck, Sanofi, Roche, Janssen; travel support: Servier, BMS, Roche, Merck, Pharmamar, Pfizer, Pierre Fabre, Sanofi, Daiichi Sankyo, Gilead; stock and other ownership interests: Guardant Health. LW: honoraria: Amgen, Astellas, BMS, Daiichi Sankyo, Merck, MSD, Novocure, Pierre Fabre, Servier; consulting or advisory role: Amgen, Astellas, BMS, GSK, Incyte, Lilly, Merck, MSD, Novocure, Pharmamar, Pierre Fabre, Roche; research funding: Novocure, Roche, Servier; travel and accommodation expenses: AstraZeneca, Janssen, Merck, Pierre Fabre, Roche, Servier; stock and other ownership interests: Guardant Health. PR: advisory board honoraria: Merck Sharp & Dohme; speaker honoraria: Gilead Sciences, Daiichi Sankyo, AstraZeneca, and GlaxoSmithKline Pharma. TW: speaker bureau and advisory board honoraria: Daiichi Sankyo, Roche, Merck, MSD, BMS, AstraZeneca, Novartis, Amgen. EW: speaker fees: Daiichi Sankyo, AstraZeneca, Roche. RG: honoraria: Celgene, Roche, Merck, Takeda, AstraZeneca, Novartis, Amgen, BMS, MSD, Sandoz, Abbvie, Gilead, Daiichi Sankyo, Sanofi; consulting or advisory role: Celgene, Novartis, Roche, BMS, Takeda, Abbvie, AstraZeneca, Janssen, MSD, Amgen, Merck, Gilead, Daiichi Sankyo, Sanofi;

research funding: Celgene, Roche, Merck, Takeda, AstraZeneca, Novartis, Amgen, BMS, MSD, Sandoz, Abbvie, Gilead, Daiichi Sankyo; travel and accommodation expenses: Roche, Amgen, Janssen, AstraZeneca, Novartis, MSD, Celgene, Gilead, BMS, Abbvie, Daiichi Sankyo; stock or other ownership: Novo Nordisk, Lilly. All other authors have declared no conflicts of interest.

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